The Power of Protein: *nPCR as a Measure of Nitrogen Balance in Hemodialysis Patients*

Introduction to Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as the slow loss of kidney function over time.[1] The Centers for Disease Control and Prevention estimates that more than 1 in 10 adults, or over 20 million people, in the United States currently have CKD.[5] The disease is categorized into five stages which are ranked by severity, the last of which is called End Stage Renal Disease (ESRD). There is no cure for ESRD, so these patients depend on renal replacement therapy, either in the form of dialysis or a kidney transplant.[1] In 2011 alone, more than 113,000 patients in the U.S. started undergoing maintenance dialysis treatments.[5]

Healthy kidneys are responsible for removing waste products and excess water from the blood.[1] When the kidneys become compromised, a patient's glomerular filtration rate (GFR) will decline. GFR is a commonly used measure of kidney damage, as it estimates how much blood is passing through the kidneys' glomeruli each minute. In other words, GFR indicates the rate at which the kidneys are able to filter water and waste from the blood.[37] The National Institute of Health diagnoses CKD in patients with a GFR <60 mL/min for 3 or more months.[4] The most common causes of CKD are diabetes and hypertension, although other diseases and conditions can also harm the kidneys. These include, but are not limited to, polycystic kidney disease, kidney stones and infections, and toxic chemicals.[1]

The consequences of CKD are many and spread throughout the body. As a result of excess fluid retention, patients with CKD develop high blood pressure, low blood cell count or anemia, and vitamin D deficiency. Bone health is also negatively impacted. Patients with ESRD typically undergo dialysis when they have only 10-15% of kidney function left.[1] Dialysis has four major roles, in which it helps to (1) remove extra salt, water, and waste products from the body, (2) maintain safe levels of minerals and vitamins, (3) control blood pressure, and (4) produce red blood cells.[2]

There are two types of dialysis, peritoneal dialysis (PD) and hemodialysis (HD). PD utilizes the peritoneum, or the membrane covering the walls of the abdomen. By inserting a catheter into the abdominal cavity and filling it with a hypertonic solution called dialysate, waste and fluids are drawn out of the blood through the peritoneum and into the solution. The waste solution is then drained from the body and disposed of.[2] This is in contrast to HD, which uses a dialyzer or "artificial kidney." In this mode of dialysis, patients are attached to a machine that passes their "dirty" blood through a dialyzer and dialysate solution. It then returns the newly filtered blood back to their bodies.[3]

Another important aspect of CKD management involves what patients are eating. Depending on the stage of CKD and/or mode of dialysis, the renal diet requires patients to monitor, and

oftentimes restrict, their intake of phosphorus, potassium, and sodium.[10] In general, CKD patients on dialysis require more protein and more calories than their non-dialysis counterparts.[9] This is in part due to the fact that 6-12 grams of amino acids, as well as other nutrients, are lost during each dialysis session. In addition, poor appetite and weight loss are common problems for chronic HD patients.[18]

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that maintenance HD patients consume at least 1.2 grams of protein per kilogram of body weight per day (g/kg/d), at least 50% of which should be of high biological value.[9] This guideline was developed in part based on studies showing that a protein intake between 1.0-1.1 g/kg/d is associated with a neutral nitrogen balance.[23] In regards to energy intake, KDOQI recommends that individuals ≤60 years old consume 35 kcal/kg/d, while those >60 years old consume 30-35 kcal/kg/d. Similar to the guidelines concerning protein intake, it is thought that this level of energy intake is adequate in terms of inducing neutral nitrogen balance and maintaining serum albumin levels.[9] Although controversial, hypoalbuminaemia, or low serum albumin, is commonly used to detect malnutrition in individuals undergoing HD.[8]

Cardiovascular Disease, Malnutrition, and Inflammation in CKD

According to a 2013 report by the U.S. Renal Data System, survival of maintenance HD patients has not improved substantially in the past two decades. In fact, almost two thirds of these patients die within five years of initiating chronic dialysis treatments. Most of these deaths are linked to cardiovascular disease (CVD).[28] It is well established that patients with CKD have a significantly higher prevalence of CVD and higher mortality than non-CKD patients.[6] The annual mortality rate due to CVD is 10- to 20- fold higher than in the general population, even when adjusted for age, gender, race, and the presence of diabetes mellitus.[7]

Malnutrition and inflammation are also very prevalent in this patient population. It is estimated that 31-77% of CKD patients are malnourished,[6] and 30-65% have chronic, low-grade inflammation.[23] In contrast to the general population, a high body mass index (BMI) is associated with better survival in ESRD patients, despite the negative metabolic effects of obesity. In other words, the protective effects of obesity on nutritional status outweigh the increased risk for insulin resistance, diabetes, coronary calcification, and atherosclerosis.[24]

Malnutrition-inflammation is thought to have both CKD-related and non CKD-related origins. Elevated levels of urea in the blood, non-sterile dialysate, bio-incompatible membranes, and vascular access infections often plague CKD patients undergoing dialysis. Chronic heart failure, tobacco use, insulin resistance, elevated fat mass, and hypertension occur in both CKD and non-CKD patients. Whatever the cause, these factors contribute to increased levels of cytokines (for example, tumor necrosis factor-α, interleukin-1, and interleukin-6) and reduced appetite and

intake. This is turn can lead to muscle wasting, weight loss, and decreased white blood cell count. Patients with moderate to severe CKD often have reduced total cholesterol as well, and studies show that low cholesterol levels in these patients consistently correlate with increased IL-1 and TNF-α levels.[6] In addition, inflammation contributes to decreased albumin synthesis by the liver and an increase in the albumin fractional catabolic rate.[18]

Much of the existing research indicates that the presence of malnutrition in CKD patients cannot be determined by a single value. Instead, a larger panel of measurements is recommended, including measures of body mass and composition, dietary protein and energy intake, and serum protein status.[20] A study by Thijssen et al. (2015) explored the benefits of using a "composite nutritional score" to diagnose malnutrition, which included serum albumin, serum phosphate, serum creatinine, equilibrated normalized protein catabolic rate (enPCR), and interdialytic weight gain (IDWG). Although the authors admit that this method requires further validation, a comprehensive score has advantages. Not only is it easier to track in practice, as opposed to following multiple clinical parameters, each component of the score represents a unique aspect of nutrition.[29]

Fouque et al. (2011) compiled 11 clinical criteria commonly used to diagnose protein-energy wasting (PEW). As illustrated in *Table 1* below, the criteria are split into four categories: serum chemistry, body mass, muscle mass, and dietary intake.[23]

Table 1: Criteria for clinical diagnosis of PEW[23]

Serum chemistry	
Serum albumin	<3.8 g/dL
Serum prealbumin	<30 mg/dL (in HD patients)
Serum cholesterol	<100 mg/dL
Body mass	
BMI	<23 kg/m^2
Unintentional weight loss	5% over 3 mo. or 10% over 6 mo.
Total body fat percentage	<10%
Muscle mass	
Muscle wasting	Reduced by 5% over 3 mo. or 10% over 6 mo.
Reduced mid-arm circumference area	>10% reduction
Creatinine appearance	N/A
Dietary intake	
Unintentional low protein intake	<0.8 g/kg/d for 2 months (in HD patients)
Unintentional low energy intake	<25 kcal/kg/d for 2 mo.

Although frequently used in clinical practice, numerous studies indicate that relying on serum proteins as markers of malnutrition is problematic. This in part due to the fact that the synthetic

rates of serum albumin, prealbumin, and retinol-binding protein are vulnerable to the effects of inflammation.[7] A study by Gama-Axelsson et al. (2012) found that serum albumin correlates with age, diabetes, and C-reactive protein (CRP) levels but less so with markers of poor nutrition, such as lean body mass and handgrip strength. Consequently, they concluded that serum albumin's reliability as a predictor of nutritional status in dialysis patients is limited. In addition, high serum albumin levels are observed even in cases of marasmus, or protein-energy malnutrition, and severe anorexia. Although this may be partly explained by albumin's long half-life (20 days) and its abundance in the body, low serum albumin levels are likely a better indication of illness as opposed to malnutrition.[25,38]

Serum prealbumin is another measure used to determine nutritional status. As prealbumin has a significantly shorter half-life (2-3 days) than albumin, it is proposed that it may be a more sensitive indicator of nutritional status and mortality risk. Chertow et al. (2000) discovered that for every 1 mg/dL increase in prealbumin there was a 6% decrease in mortality risk. In addition, they found that the risk of death increased in individuals with serum prealbumin <25 mg/dL, regardless of whether serum albumin was high or low.[26]

Although serum prealbumin may predict survival in maintenance HD patients, it has also been shown to decrease in the presence of inflammation. Therefore, the usefulness of both albumin and prealbumin as discrete markers of malnutrition is undermined by the fact that they reflect acute phase reactants in addition to the visceral protein pool.[26]

Examining the Utility of normalized Protein Catabolic Rate

Although difficult to measure, low dietary protein intake is associated with an increased risk of death among HD patients. Consequently, a variety of equations have been developed in order to estimate protein intake in this population. Protein catabolic rate (PCR), also known as protein equivalent of nitrogen appearance (PNA), is defined as the rate of increase in serum urea nitrogen levels between two HD treatments. In other words, it compares the levels of urea nitrogen in the body before and after dialysis.[11] PCR is expressed as grams of net protein degradation per kilogram of body weight per day (g/kg/d), and can therefore be loosely interpreted as an estimate of dietary protein intake. Although there are numerous equations used to calculate PCR, it is most commonly calculated using Kt/V, a measure of dialysis adequacy, and both pre- and post- dialysis blood urea nitrogen concentrations (BUN).[12]

The following equation was specifically developed for patients undergoing HD three times per week. It includes an additional factor K_R, or a measure of residual renal clearance, as well as constants *a* and *d*, which are specific to each dialysis session of the week.[35] Residual renal function is important to take into account, as nPCR will be underestimated otherwise.[36] The factor 0.17 is derived from the inclusion of urea generation rate and a normalization factor, or

[V_{urea}/0.58]. The mean urea distribution volume [V_{urea}] is divided by 0.58, as the percentage of water in lean body mass is approximately 58%.[35] The normalization coefficient is meant to represent the patients' ideal body weight, as opposed to their actual body weight. This allows for comparison of nPCR values among patients over a wide range of body sizes.[35,36] The equation by Garred et al. (1997) is as follows:

$$nPCR = a\left[\frac{Kt}{V} + d\frac{K_R}{V}\right]\left(BUN_{pre} + BUN_{post}\right) + 0.17$$

Therefore, normalized PCR (nPCR), reported in grams of urea nitrogen per kilogram per day, is considered to be a marker of steady-state protein intake in stable HD patients.[29] Patel et al. (2000) followed 17 HD patients over 8 months and found that dietary supplement use in stable, chronic HD patients significantly increased both nPCR and total protein intake.[14] Studies also show that a low nPCR typically reflects decreased dietary protein intake, while a very high nPCR may indicate tissue catabolism.[29] Kim et al. (2013) examined correlates of low serum albumin (defined as <3.8 g/dL), including markers of dietary intake and inflammation. They found that the concentration of serum albumin increases with increasing nPCR up to around 1.4 g/kg/d, at which point albumin drops off.[17]

Although nPCR allows for comparison among patients over a wide range of body sizes, it is only a single pool measurement; therefore, nPCR may overestimate urea clearance. Equilibrated nPCR (enPCR), on the other hand, is a double pool measurement that incorporates the impact of "urea rebound." In other words, enPCR accounts for urea in the intracellular space as well as in the extracellular space, or circulating blood volume. It is slightly lower than nPCR, and is thought to provide a more accurate picture of protein breakdown.[34,36] It should be noted that most of the existing literature has only examined nPCR, despite the use of enPCR in clinical practice.

In Support of normalized Protein Catabolic Rate

Many studies have attempted to determine the usefulness of PCR and nPCR in predicting protein intake, nitrogen balance, and mortality in maintenance HD patients. Shinaberger et al. (2006) followed a two-year cohort of 53,933 maintenance HD patients from DaVita clinics across the U.S. in order to determine the effects of low protein intake on mortality risk. Comorbidities, dialysis dose and adequacy, nPCR, and available markers of malnutrition-inflammation were all considered in the analysis. They found that both a low dietary protein intake (<0.8 g/kg/d) and a decrease in intake over time are associated with increased mortality, and concluded that the best survival is linked to nPCR values of 1.0-1.4 g/kg/d.[13] Similar to findings by Kim et al. (2013), they determined that a nPCR of >1.4 g/kg/d is associated with greater mortality.[13,17]

A study by Segall et al. (2009) also found decreased nPCR to be a risk factor for death. For every 0.1 g/kg/d increase in nPCR, death risk decreased by 15%. Advanced age (>55 years old), a

lower subjective global assessment (SGA) score, and diabetes were also determined to significantly increase patients' risk of death.[15] The SGA is a widely used assessment tool that uses 5 components of medical history (weight change, dietary intake, gastrointestinal symptoms, functional capacity, disease and its nutritional requirements) and 3 components of a physical examination (signs of fat and muscle wasting, alternations in fluid balance) to evaluate nutritional status.[39] This study's reliability is limited by its sample size; it followed a total of 149 maintenance HD patients at one dialysis center in Romania.[15]

Ravel et al. (2013) examined the association between PCR, nPCR, and mortality. This 8-year prospective cohort study followed 98,489 maintenance HD patients across the U.S. They found that a low PCR (<30 g/kg/d) is associated with higher all-cause mortality, even after controlling for a variety of demographic and laboratory variables (age, gender, serum albumin, diabetes, race/ethnicity). Similar to other studies, they also found that a very high nPCR (>1.3 g/kg/d) is associated with increased all-cause mortality. The authors of this study suggest the later result may be a consequence of the toxic effects of a very high-protein diet, or a hypercatabolic state due to inflammation. Other explanations include a confounding effect of low body weight or poor compliance to medical prescription.[28]

A prospective cohort study by Kalantar-Zadeh et al. (2003) found that both nPCR and serum albumin predict hospitalizations and mortality in HD patients with adequate or high Kt/V (defined as >1.20). The authors included Kt/V in the analysis in order to rule out other, potentially confounding, causes of the correlation between low nPCR and poor outcomes; for instance, uremia, low Kt/V, or the mathematic coupling of nPCR and Kt/V. 122 HD patients from a single dialysis unit were evaluated, all of whom had been undergoing treatment for one month to 17 years. Low nPCR and serum albumin levels were each found to have statistically significant correlations with mortality, as well as total days of hospitalization, total number of hospitalizations, and time to first hospitalization.[16]

Lukowsky et al. (2014) followed a cohort of 17,445 incident HD patients at one DaVita clinic for the first two years of dialysis therapy. In order to account for serum albumin's relationships to both nutritional status and inflammation, they categorized patients into four groups: (1) high nPCR and low serum albumin, (2) low nPCR and high serum albumin, (3) low nPCR and low serum albumin, and (4) high nPCR and high serum albumin. The authors hypothesized that nPCR correlates more closely with nutritional status than does serum albumin. Similar to Kalantar-Zadeh et al. (2003), they found that low serum albumin (<3.5 g/dL) and low nPCR (<1.0 g/kg/d) are consistently associated with high mortality. In addition, they found that a 0.2 g/kg/d rise in nPCR shows a reverse effect on mortality, but only for the first 6-9 months. The authors suggest that very high nPCR values (>1.4 g/kg/d) or a rapid increase in nPCR may indicate negative nitrogen balance, an increased catabolic rate due to infection, or inflammation.

Therefore, they suggest close monitoring and evaluation for PEW in patients with an elevated nPCR, decreased serum albumin, decreased serum creatinine, and weight loss.[18]

Limitations of normalized Protein Catabolic Rate

Numerous other studies highlight the limitations of using nPCR in clinical practice. Shinaberger et al. (2006) points out that the associations between nPCR and mortality decrease substantially when the results are adjusted for markers of malnutrition-inflammation. Consequently, it is unclear whether the relationship between protein intake and survival is caused by, or is a consequence of, anorexia secondary to malnutrition-inflammation.[13] In addition, nPCR does not differentiate between protein derived from dietary sources and that derived from catabolism of endogenous proteins.[22]

Another major critique of nPCR is that it is only considered a valid indicator of protein intake under steady-state conditions. In other words, it does not accurately reflect protein intake in patients who are under- or over- nourished, or in a state of fluid imbalance. In addition, Kim et al. (2013) suggests that nPCR may in fact overestimate protein intake in inflammatory states due to increases in nitrogenous protein breakdown.[17] Other studies point out that some nPCR calculations fail to take all nitrogen lost into account. The nitrogen in urea, creatinine, and uric acid is only about 94% of total nitrogen lost; there is also some nitrogen lost through skin, breathing, and urine. Although many ESRD patients stop urinating all together, this may affect those HD patients with residual renal function. In addition, more amino acids and protein are lost into the dialysate solution as a result of dialyzer reuse, a practice that is still utilized by some dialysis clinics.[19]

It has also been shown that nPCR is in part determined by other dialysis-related measures not considered in the calculations. Bastani et al. (1996) retrospectively reviewed the charts of 70 HD patients in one dialysis unit and found that moderate to severe reductions in serum concentrations of bicarbonate significantly impact protein catabolism in stable HD patients. Along with underscoring the importance of maintaining normal acid-base homeostasis in these patients, this finding indicates that variables other than protein intake affect nPCR. The authors also found that changes in dialysis delivery and adequacy (measured by Kt/V) and uremia (measured by mid-week BUN) are independent determinants of nPCR.[22]

A study by Kloppenburg et al. (1999) found that a single nPCR measurement is unreliable when assessing dietary protein intake. The authors evaluated 50 stable HD patients and discovered that a mean of three nPCR values correlates significantly with protein intake, while there is a notable lack of correlation between a single nPCR value and dietary protein intake. Dietary protein intake was estimated with 7-day food records and averaged over the entire week. Therefore, due to session-to-session variations in the urea reduction ratio (URR), Kt/V, and urea distribution

volume, a single nPCR measurement will give an inaccurate picture of a patient's true protein intake.[21]

Lastly, there is debate over how nPCR is calculated from PCR. In theory, the patient's dry body weight is close to his or her ideal body weight and will therefore preserve a body composition ratio of approximately 0.73 (lean body mass to dry body weight).[30] In reality, this is not always the case, and so numerous other equations have been developed, using standard body weight, adjusted body weight, or body weight derived from urea distribution volume.[35] In conclusion, nPCR can be misleading in obese, malnourished, or edematous individuals due to a skewed ratio of lean body mass to dry body weight.[17,35]

Implications for Practice

In order to gain real-time perspective on the utility of enPCR in clinical practice, I first asked three dietitians at hemodialysis clinics in the Minneapolis-St. Paul area the following question: *How useful do you feel enPCR is in predicting protein intake and protein-energy malnutrition in maintenance HD patients?* Two main themes emerged from these conversations. Firstly, the dietitians expressed that they do not feel well informed on enPCR, in terms of how it is defined, how it should be interpreted, or how it is calculated. Overall, they have received minimal education regarding enPCR; therefore, they typically provide patients with a brief explanation only when asked. Secondly, they do not feel confident using enPCR as an indication of patients' protein intake, due to its many limitations. As one of the dietitians pointed out, a large percentage of patients at her clinics are either fluid overloaded or obese.

Regardless of the extent to which enPCR is actually utilized, it is tracked on a month-to-month basis in many dialysis clinics. It is also shown on the monthly lab reports reviewed with patients alongside serum albumin, the primary malnutrition marker used by renal dietitians. The "ideal" enPCR for HD patients is considered to be 1.14 g/kg/d.[36]

I then conducted a mini-analysis with a sample of 30 maintenance HD patients. A total of 15 men and 15 women, with an average age of 60 years, were randomly selected from one Fresenius Medical Care dialysis clinic in the Minneapolis-St. Paul area. Results were compiled into *Table 2*. Names and other patient identifiers were removed from all anthropometric and biochemical data in order to protect patient privacy. All enPCR values were ranked from lowest to highest and split into three sections: (1) <0.8 g/kg/d, (2) 0.8-1.3 g/kg/d, and (3) >1.3 g/kg/d. In addition to enPCR, nPCR, and serum albumin, information regarding body weight, fluid gains, and nutritional status was also collected. The malnutrition risk score is a comprehensive score that is determined by a combination of factors. These include unplanned weight loss, current visceral protein stores (measured by serum albumin levels), appetite and/or current intake, and frequency of symptoms affecting intake (whether they be gastrointestinal, medication-related, or

psychosocial factors). My personal experience at this HD clinic indicates that dietitians most closely monitor those patients with the lowest serum albumin and malnutrition risk scores.

Table 2: Comparisons of enPCR, nPCR, & Serum Albumin in 30 HD Patients

enPCR (g/kg/d)	nPCR (g/kg/d)	Serum Albumin (g/dL)	Age (yrs)	Gender	BMI (kg/m^2)*	Average % IDWG	Malnutrition Risk Score**
0.53	0.58	3.9	62	F	25	1.7	15
0.62	0.66	3.1	54	F	35	3.1	9
0.63	0.69	3.9	42	F	17	5.0	14
0.64	0.67	4.0	68	M	28	3.8	16
0.66	0.68	4.3	65	M	29	3.6	16
0.69	0.73	4.4	64	M	25	2.6	16
0.72	0.77	4.0	87	M	33	2.3	16
0.72	0.79	4.2	71	M	24	3.7	16
0.73	0.78	3.9	56	F	33	1.2	15
0.74	0.78	4.0	63	M	21	3.4	15
0.75	0.79	4.2	43	F	35	2.5	13
0.76	0.82	3.3	69	M	28	2.0	15
0.79	0.83	3.3	78	F	26	3.5	14
0.85	0.93	3.2	66	M	28	2.8	15
0.89	0.94	4.1	50	F	20	2.0	15
0.92	0.99	3.8	72	M	28	2.7	14
0.93	1.00	4.2	40	F	17	3.4	16
0.94	1.02	4.0	64	M	28	2.1	15
0.95	1.00	3.5	87	F	21	3.0	11
0.99	1.03	3.2	60	F	31	3.5	13
1.01	1.09	4.1	56	M	35	4.0	14
1.03	1.12	3.8	47	M	26	2.2	15
1.06	1.12	4.1	57	M	31	4.9	16
1.25	1.32	3.7	35	M	23	3.4	9
1.28	1.34	4.0	26	F	34	3.8	15
1.31	1.37	3.6	72	M	24	4.5	10
1.33	1.40	3.6	68	F	22	2.7	14
1.40	1.49	4.1	43	F	22	4.4	15
1.53	1.60	3.9	75	F	29	2.9	13
1.56	1.81	4.0	53	F	21	4.2	15

*BMI categories: <20 = malnutrition; 20-24 = ideal; 25-27 = overweight; >27 = obesity

**Malnutrition risk score defined as follows: 14-16 = well-nourished; 11-13 = mild malnutrition risk; 8-10 = moderate malnutrition risk; ≤7 = severe malnutrition risk

Examining *Table 2*, no clear trends can be seen between enPCR and any of the other variables. If enPCR is truly an indication of protein intake in HD patients, one might expect to see a correlation between lower malnutrition risk scores and lower enPCR values, but this is not the case. In addition, serum albumin levels of 4.0 g/dL and higher can be seen in all three of the enPCR categories. This calls into question the ability of enPCR to predict mortality risk, despite what previous studies have shown.

As indicated in the existing literature, enPCR is a less accurate measure in patients who are obese, otherwise nutritionally compromised, and/or gaining too much fluid in between HD treatments. Therefore, patients meeting the following criteria were excluded from further analysis: (1) BMI >27 kg/m^2, (2) average IDWG ≥5%, and/or (3) malnutrition risk score ≤13. The data for the remaining 11 patients, who are considered to be more "stable," is shown below in *Table 3*.

Table 3: Comparisons of enPCR, nPCR, & Serum Albumin in 11 Stable HD Patients

enPCR (g/kg/d)	nPCR (g/kg/d)	Serum Albumin (g/dL)	Age (yrs)	Gender	BMI (kg/m^2)*	Average % IDWG	Malnutrition Risk Score**
0.53	0.58	3.9	62	F	25	1.7	15
0.69	0.73	4.4	64	M	25	2.6	16
0.72	0.79	4.2	71	M	24	3.7	16
0.74	0.78	4.0	63	M	21	3.4	15
0.79	0.83	3.3	78	F	26	3.5	14
0.89	0.94	4.1	50	F	20	2.0	15
0.93	1.00	4.2	40	F	17	3.4	16
1.03	1.12	3.8	47	M	26	2.2	15
1.33	1.40	3.6	68	F	22	2.7	14
1.40	1.49	4.1	43	F	22	4.4	15
1.56	1.81	4.0	53	F	21	4.2	15

Similar to *Table 2*, the data in *Table 3* fails to show a relationship between enPCR and serum albumin, or enPCR and malnutrition risk. It should be noted that this analysis has numerous limitations, particularly its small sample size and a lack of enPCR trends over time. In addition, it would be strengthened immensely by the inclusion of actual dietary protein intake (measured with food records, food frequency questionnaires, or 24-hour recalls), as well as weight trends (measured by % body weight gained or lost over time). Nevertheless, it does not support the usefulness of enPCR in practice.

Interestingly, Fresenius Medical Care has provided its dietitians with enPCR interpretation tools (for an abbreviated version refer to *Appendix A)*, although my observations indicate that they are

rarely utilized. It should also be noted that the tool is only appropriate for patients who have a stable dry weight and a stable albumin level of ≥3.8 g/dL. Patients who are classified as "unstable" require a close evaluation of enPCR alongside numerous other parameters (such as co-morbidities, protein status, CRP, dry weight), making its interpretation much more complicated.[36]

Discussion

Despite advances in medical knowledge and technology, malnutrition and PEW remain prevalent problems in the HD patient population. There are many challenges associated with achieving ideal protein intake in dialysis patients, largely because their nutritional requirements are so much higher than those of the general population. A study by Ekramzadeh et al. (2014) randomly selected and interviewed 255 patients from three dialysis centers. All patients were on HD for at least 3 months without acute illness, and nutritional status was measured using both SGA and malnutrition-inflammation scores. After exploring numerous medical, behavioral, and socioeconomic barriers, the authors determined that poor appetite, depression, difficulty chewing, poor nutrition and protein knowledge, and the need for help with shopping and cooking are all independently and significantly correlated with malnutrition.[27]

Fortunately, it has been shown that at least some cases of poor protein intake and PEW can be reversed with aggressive supplementation.[23] Although patients with evidence of ongoing inflammation are less likely to respond to nutritional support, research suggests that supplementation should still be attempted.[8,33] Recent studies indicate that nutritional supplements, administered orally, enterally, or parenterally, are effective in replenishing both protein and energy stores in HD patients who are unable to maintain adequate dietary intake from meals alone.[33]

Due to the pervasiveness of malnutrition in the HD population, it is important to understand the utility of nPCR, as well as other nutrition-related laboratory values. Further research is required before nPCR can play a truly valuable role in clinical practice, as indicated by the inconclusiveness of the above literature review. Numerous studies indicate that an nPCR between 1.0-1.4 g/kg/d is significantly correlated with a decreased risk of death in stable maintenance HD patients.[13,15,16,18,28] That said, it is only reliable in patients with a dry weight that is close to their ideal body weight; in other words, those who are within 95-115% of standard body weight.[17,35] This significantly limits the number of patients for which nPCR may be helpful; as illustrated in *Table 2* and *Table 3* of the mini-analysis, 50% of the subjects were classified as obese and therefore did not meet this criteria.

In addition, none of the dietitians I interviewed regularly use nPCR in practice, as they feel as though it does not accurately reflect their patients' protein intake or overall nutrition status. This

is despite the fact enPCR is a value that renal dietitians are expected to positively influence; it is even included on patient reports. Therefore, my personal experience in HD clinics aligns with the findings from the mini-analysis, which indicate that enPCR may not be of much use after all. More often than not, the enPCR value was irrelevant with regards to the patient's plan of care. Instead, dietitians focused their efforts on the patient's serum albumin, reported dietary protein intake, and physical appearance. These were the factors used to determine which nutritional interventions would be most effective and most beneficial for the patient, not enPCR.

The conflicting evidence regarding nPCR and enPCR remains a dilemma for renal dietitians, as there is a disconnect between what the literature implies and what is seen in clinical practice. Therefore, it can be concluded that nPCR is not a reliable indicator of protein intake or mortality in HD patients. Outstanding questions include:

- Is nPCR more reliable if interpreted in conjunction with one or more measures of nutritional status (for instance, the presence of muscle wasting, serum prealbumin, and/or a SGA score), as opposed to standing alone?
- Is there a correlation between nPCR and other scientifically proven, reproducible measures of dietary protein intake (for instance, 24 hour recalls) and/or nutritional status (for instance, bioimpedance spectroscopy)?
- It is well established that malnutrition is related to both inflammation and CVD[28,23]. To what extent is nPCR influenced by the presence of inflammatory factors (for example, what is its relationship to CRP or TNF-α)?
- Should additional variables be included in the equations used to calculate nPCR; for instance, to account for whether a dialyzer is used once versus used multiple times?
- Almost all of the existing literature exploring nPCR involves *stable* HD patients. Further research is needed in order to understand how well nPCR estimates protein intake and mortality in *unstable* HD patients, as these patients are typically those most at risk for poor intake and malnutrition.

Researchers and health care providers alike have identified PEW as both a serious and persistent problem for maintenance HD patients.[27] Consequently, it often falls on the shoulders of renal dietitians to address protein intake with their patients, in order to maintain or even improve nutritional status. Unfortunately, nPCR currently falls short as a method of estimating dietary protein intake in this patient population. Until further research examining the utility of nPCR has been completed and its limitations have been addressed, dietitians should continue to rely on other measures when assessing malnutrition in HD patients. Using dietary recalls, physical examinations, and better-supported laboratory values, dietitians can help their patients achieve a protein intake that replenishes the protein lost during each dialysis treatment, preserves lean body mass, and decreases risk of death.

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Appendix A: Interpretation of enPCR in Stable HD Patients[36]

enPCR (g/kg/day)	*Interpretation*	*Intervention*
<0.8	• Low protein intake • Mild negative nitrogen balance • May indicate unmeasured residual renal function	• Counsel patient to increase protein & calorie intake to recommendations • Begin supplements
0.8-1.3	• Adequate protein intake • Neutral nitrogen balance	• Encourage patient to continue current intake
>1.3	• Excessive protein intake OR • Severe catabolism	• Consider increasing dialysis dose to support a higher protein intake • If catabolic, counsel patient to increase protein & calorie intake to recommendations and begin supplements